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REMARKS

This timely reply is to the Office Action dated July 26, 2005. Claims 1, 2, 4-8, 10, 11, and 13-19 were pending and all claims were rejected. Claim 1 is amended, claim 8 is cancelled and new claims 20 and 21 are presented.

In a phone interview on October 18, 2006 with the Examiner, the registered advocate for the Applicant agreed to amend claim 1 and present portions of claim 1 in a new claim to avoid other potential ambiguities of claim 1 in its rejected form. Applicant appreciates the constructive impute from the Examiner.

In the office action claim 1 was rejected under 35 U.S.C. 112, second paragraph as being indefinite.

Examiner stated:

2. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites a "to skin or other tissue surface external to the body of the mammal". The meaning of "other tissue surface external to the body of the mammal" is not clear. An explanation is required.

During the phone interview of October 18, 2006 it was agreed to amend claim 1 to recite specific tissue surfaces consistent with the specification to avoid the ambiguity of the phrase "to skin or other tissue surface external to the body of the mammal". The relevance of reciting an "increase the subepithelial partial pressure" with respect to an organ was also questioned by the Examiner during the phone interview. The application of the superoxygenated composition to an organ is presently recited in new claim 20 which recites organs without dependence of an epithelial cell surface and is consistent with the specification. Claims 1 and 20 are copied below for convenience.

Claim 1 A method of increasing tissue oxygenation in mammals, comprising applying a superoxygenated composition of oxygen microbubbles consisting essentially of oxygen in a pharmaceutically acceptable vehicle directly to a tissue surface selected from the group consisting of skin or mucous membranes for a time sufficient to increase the subepithelial partial oxygen pressure from about 30% to about 120% above baseline pO_2.

Claim 20 A method of increasing tissue oxygenation in mammals, comprising direct application of a superoxygenated composition of oxygen microbubbles consisting essentially of oxygen in a pharmaceutically acceptable vehicle to an exposed or removed mammalian organ to increase the tissue oxygenation.

Support for amended claim 1 is found in line 22 page 4 through line 5 page 5 and line 16 through line 22 page 12 of the present application. Support for new claim 20 is found in line 22 page 4 through line 5 page 5 of the present application.

In the Office Action the Examiner concluded that claims 1, 2, 4-6, 8, 10, 11, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by White US 4,366,169.

About White, Examiner stated:

White discloses a method of treating a wound involves contacting the wound with a molecular oxygen containing member of a family of materials popularly known as synthetic blood or blood substitutes (col. 2, lines 61+) and the carrier comprises water (col. 4, line 43). Among the skin problems treated by the method are burns (col. lines 50+). Oxygen can be added to the material by many different means; one example of which would be to bubble 100% oxygen through the material (col. 4, lines 37+). White teaches that Burns are the primary example and healing of damaged tissue

characteristic of burns can be accelerated by increasing the amount of oxygen at the damaged tissue. Oxygen tents surrounding the entire victim or the burn area (hyperbaric chambers) have been used but not overly successfully because they present safety problems, the exchange rate of the oxygen and damaged tissue is not remarkably better, and they do not always eliminate bacterial infections which are prone to occur during the healing period. Accordingly, the invention as increasing the concentration of oxygen in the burned area will consequently improve the bacterial infection. White adds that Contacting as used herein refers to a local application and excludes the use of perfluorocarbons in the blood system (col. 5, lines 45+). In addition, the reference discloses that The contacting in most cases will be by application to the skin surface, as described before, but does not exclude application to non-skin surfaces by means other than the blood system. Examples of the latter applications include applications to respiratory mucous surfaces by tubes, etc., and the like (col. 5, lines 49+), and explains that the ability to transport oxygen is related to the solubility of oxygen in the materials and suggest that the perfluorinated materials will absorb 10-100 cc of oxygen per 100 cc of material at 25°C. and 760 milliliters of mercury. The substantially fluorinated carbon materials, i.e., perfluorocarbons, which can be used with this invention will have similar oxygen transport abilities (col. 4, lines 15+). The contacting of a burn victim with the perfluorocarbon can occur by various means. For example, one embodiment involves the immersion of the victim in a bath of the material maintained at a suitable temperature for the victim's comfort (col. 4, lines 65+), the disclosure reads on the recitation of the temperature of instant claim 11 of a temperature between 0 and 34°C, this temperature encompass a comfortable bath

temperature, and also reads on the whirlpool bath of instant claim 17 because according to white, the bath should be recirculated through cleansing means which suggest a simulation of a whirlpool with agitation. The vehicle can be in the form of a gel or a spray (claim 17).

Note that the instant application defines The superoxygenated compositions of the present invention as comprise at least about 55 ppm oxygen but find useful concentrations from about 45 to about 220 ppm. The oxygen level in the compositions depends on several factors, including the type of composition, the temperature, and other components, active or not, that may be added for various reasons such as stability, ease of application or to enhance absorption [0020]. Accordingly, White's composition reads on the instant definition.

Also the limitation of time sufficient to increase the subepithelial partial oxygen pressure from about 30% to about 120% above baseline pO_2 is considered inherent since the disclosed method of the prior art would cause the same effect on healing of the wound or burn.

According to the Examiner, White discloses a method of treating a wound with a "molecular oxygen containing member of a family of materials known as synthetic blood or blood substitute". This family of synthetic blood materials has a carrier that is perfluorocarbons as the indicated in the title of White "Use of Perfluorocarbons as Wound Treatment" or as indicated in claim 1 of White "substantially fluorinated carbon material or a mono or dibrominated derivative thereof having an ability to transport oxygen". In a passage referred to, and partially quoted by the Examiner, col. 4 line 14+ "the ability to transport oxygen is related to the solubility of oxygen in the materials and suggest that the perfluorinated materials will

absorb **10-100 cc of oxygen per 100 cc of material at 25° C. and 760 milliliters of mercury"**. The recitation of molecular oxygen indicates that oxygen is dissolved in molecular form rather than in atomic form, as atomic oxygen is the form of oxygen involved in some absorption processes. The recitation of molecular oxygen does not indicate or imply that the oxygen is in a gaseous state; rather, as indicated above, oxygen is dissolved.

Applicant respectfully submits that the dissolved oxygen of White is quite distinct from the superoxygenated composition of the present claimed invention, and because of this difference White cannot anticipate the present invention. The present invention does not include significant amounts of dissolved oxygen, rather the superoxygenation composition results from oxygen residing in microbubbles dispersed in a pharmaceutically acceptable vehicle. White does not recite a microbubble. It is the form of an O_2 microbubble with a diameter that is micro to nanometer in size, as characterized in Fig. 3, dispersed in a liquid vehicle that makes the superoxygenated composition so effective at oxygenating tissue, not the absolute quantity of oxygen in the composition. The superoxygenated compositions of the present invention are up to about 220 ppm O_2. The superoxygenated composition, where the vehicle is water, as in claim 13 of the present invention, has a level of O_2 up to 220 ppm, as in claim 10 of the present invention. This level of oxygen would be approximately 1,500% of the maximum dissolvable O_2 at 0° C, which is higher than the maximum at 25° C. The characterization of the composition as superoxygenated is in reference to levels of O_2 relative to normally dissolved O_2 in the liquid vehicles, such as water, and not to the absolute level of O_2 in the composition. Even the lowest claimed level of O_2 of 45 ppm would have approximately 300% of the maximum dissolvable O_2 at 0° C and is considered superoxygenated. The liquid containing molecular oxygen of White, which are approximately 100,000 to 500,000 ppm O_2 by volume, would not be meet the

definition of being superoxygenated even though the O_2 levels are extremely high as these levels are for dissolved oxygen. White does not disclose a liquid containing molecular oxygen present at levels that exceed the solubility of O_2 in the fluorocarbon. Even when the solubility of O_2 in a liquid is extremely high but the liquid is not supersaturated in O_2, the release of O_2 does not necessarily occur, as it is the relative affinity of O_2 in the two media and the ability to transport the O_2 into the O_2 deficient media that is important for partitioning between the two media. As the superoxygenated composition of the present invention contains O_2 dramatically above the levels of dissolved O_2, it can readily release its O_2 to a deficient media, tissue, and the form of microbubbles provides the ability to readily transport the O_2 into that media. Therefore, White does not disclose a superoxygenated composition and can not anticipate a method that employs a superoxygenated composition comprising oxygen microbubbles.

The superoxygenated composition of the present invention is also physically different that the "molecular oxygen containing member of a family of materials known as synthetic blood or blood substitute" of White. As the O_2 is dissolved in White, O_2 is present in a continuous liquid medium. As the O_2 is in microbubbles in the instant invention, O_2 is present primarily in a discontinuous gas medium dispersed in a liquid. As White does not disclose microbubbles, but rather dissolved O_2 it cannot read on the claimed superoxygenated composition of oxygen microbubbles of the present application. Employment of a dissolved gas can not anticipate the employment of a gas dispersed in a liquid.

According to the Examiner, the carrier of White comprises water. Applicant respectfully disagrees with this assessment. No claims include water as a possible carrier and the claimed and disclosed carrier is the perfluorocarbon. White discloses water in the specification (col 4 ln 3) for an emulsion with the carrier perfluorocarbon. Water does not contain high levels of O_2,

the O_2 remains dissolved in the perfluorocarbon, which is the carrier. Again, even with water present in a liquid-liquid emulsion with the carrier, it does not modify the substantially fluorinated carbon material containing molecular oxygen in a manner that the liquid can be defined as being superoxygenated.

Applicants respectfully submit that the superoxygenated compositions of oxygen microbubbles is patentably distinguishable from the substantially fluorinated carbon material containing molecular oxygen of White. Therefore, White cannot anticipate the present invention, and request that claims 1, 2, 4-6, 10, 11, and 13 be allowed.

In the Office Action the Examiner concluded that claims 1, 2, 4-8, 10, 11, and 13-19 are rejected under 35 U.S.C. 102(b) as being unpatentable over White US 4,366,169 in view of Ladin US 5,792,090 further in view of Kolta US 6,139,876.

The Examiner states with respect to White:

White is applied as discussed hereinabove.

White does not specifically disclose use of the method to treat anaerobic bacteria, the oxygen bubble size.

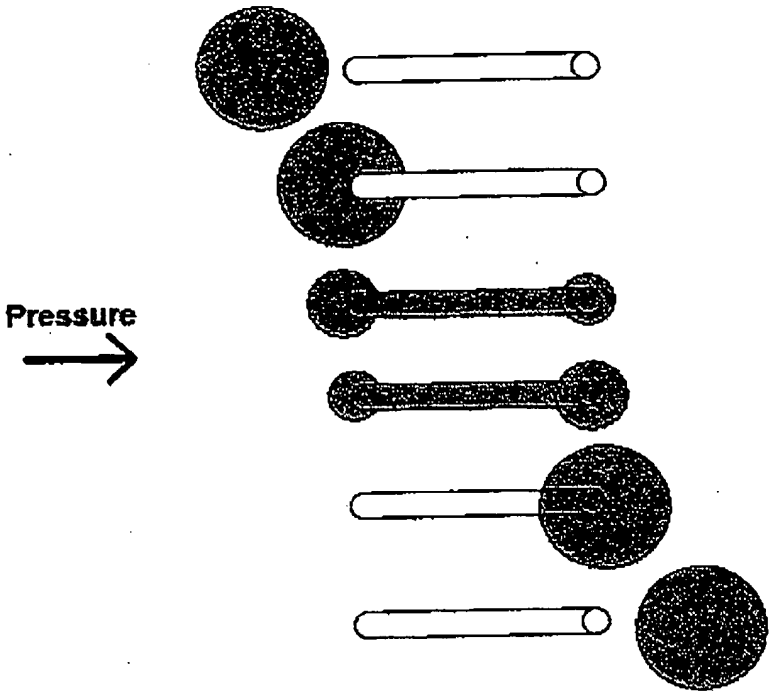
With respect to White the Examiner concedes that White does not disclose the oxygen bubble size of the present invention. Applicant respectfully submits, as indicated in detail above, that White does not disclose a composition with bubbles, which is why no bubble size is disclosed.

The Examiner states with respect to Ladin:

Ladin discloses a method of healing of surface wounds, including burns, which is facilitated by increasing the wound oxygen tension through the application of an oxygen-generating wound dressing which renewably and non-sustainingly chemically generates oxygen. The wound dressing contains an oxygen permeable membrane and an oxygen supply solution. Because the oxygen chemically produced by the subject invention may include both gaseous oxygen as well as dissolved oxygen, the membrane pore sizes of from 0.01 to 10 micron, preferably 0.1 to 1.0 microns are preferred to limit the oxygen passage (col. 5, lines 16+)

With respect to Ladin the Examiner states "Because the oxygen produced by the subject invention may include both gaseous oxygen as well as dissolved oxygen, the membrane pore sizes of from 0.01 to 10 micron, preferably 0.1 to 1.0 microns are preferred to limit the oxygen passage." Applicant respectfully disagrees with the interpretation of the section (col. 5, lines 16+) which discloses the use of the membranes. These membranes are to prevent transport of solid catalyst and dissolved salts, where it indicates removal of anionic and cationic species by absorption on the membrane, and to isolate pathogens greater than 0.45 microns, which is a restriction based on a non deformable particle size. Membranes of the type disclosed in Ladin will not stop any gas from being transported through the membrane from a high pressure side to a low pressure side, nor will it define a size of a bubble of a gas as it will not inherently provide a sheering force at the exit of the pore to break a large bubble into a small bubble. The gas transmissive abilities referred to in Ladin (col. 5 line 21) is necessarily relative to the rate at which gas can pass through the membrane and does not define an ability to define the size of a bubble. The pore size is the diameter of an open ended void through the membrane, and does not define the diameter of a deformable gas sphere that can pass through the pore. As with all membranes, any non-absorbed liquids and gases can deform to the shape of the pore and pass through the pore as illustrated below for a single large gas bubble encountering a single pore of a membrane. Therefore, the pore size cannot define the diameter of the bubble. As disclosed in Example 1 of Ladin, oxygen gas is generated and it is not in the form of a microbubble stable at ambient pressure as the pressure in a test apparatus rose to 5 atmospheres. Hence, Ladin can not

be combined with White to teach that a microbubble is formed, as no microbubble is formed and the gas can not be partitioned into microbubbles by the membrane of Ladin.



Transfer of a gas bubble through a pore of a membrane

Neither White nor Ladin teach or suggest that having oxygen in the form of a microbubble can be effective at increase the subepithelial partial pressure of oxygen. Furthermore, neither White nor Ladin demonstrates that the oxygen of their composition can pass through an epithelial layer. White claims treating a victim having a wound the normal healing of which is accelerated by exposure to oxygen, which comprises contacting the wound. White does not disclose passage of oxygen into the tissue to which the blood substitute is exposed. The wound dressing of Ladin is intended "to provide oxygen levels similar to those produced by moderate hyperbaric oxygen treatment" (col 3 ln 17-20) where hyperbaric oxygen treatment is stated to be a treatment where "the relative oxygen concentration of the deep dermis (1.8-2.2 mm) is unchanged" (col 1 ln 46-52). Hence, Ladin teaches away from expecting a surface treatment to increase subepithelial levels of O_2 when treating skin. Again the

combination of White with Ladin cannot suggest the novel ability of microbubbles to pass through epithelial tissue as has been observed for the microbubbles of the present invention.

The Examiner states with respect to Kolta:

Kolta discloses a gelatin with increased oxygen content for pharmaceutical, cosmetic and/or veterinary use. The gelatin comprises a gelling agent and a solvent, furthermore oxygen in a substantially even distribution with a pressure exceeding normal atmospheric pressure (abstract). Kolta teaches that gelatin and the oxygen encapsulated therein will have special synergetic effects. The intensive presence of oxygen will prevent proliferation of anaerobe bacteria which otherwise would rapidly multiply in the gelatin (col. 2 line 12+)

Accordingly, it would have been obvious to one skilled in the art at the time the invention was made to expand the teaching of White by realizing a fine size of the oxygen bubbles because the size of the bubble relate inversely with the penetration of the tissue and also to ensure the effect of the method on the anaerobic bacteria because Kolta discloses that the presence of oxygen ensures the prevention of proliferation of anaerobic bacteria. The expected result would be a method for increasing skin oxygenation by applying a composition of high oxygen concentration to a wound, or burn in a topical application or a bath.

With respect to Kolta, the Examiner states that Kolta discloses that a substantially even distribution with a pressure exceeding normal atmospheric pressure. According to the abstract of Kolta, "the surface tension of the gelatin is sufficiently high to retain at least a portion of the overpressure of the oxygen throughout a predetermined period of time after having been exposed ton atmospheric environment." This overpressure can not be significant. Consider the example of a soap balloon, which has a surface tension in the proximity of that one would expect with a liquid gelatin, the pressure differential on the inside of the bubble is not significantly greater than

that of the air for the bubble to expand. As indicted above considering White, the amount of oxygen is not as important a factor for oxygenation of tissue as having oxygen in excess of the equilibrium solubility in the carrier which is possible in the present invention due to the size of the microbubbles. The bubbles that form in the gelatins of Kolta are not microbubbles that have micrometer or nanometer dimensions. Microbubbles would not result in the scattering of light at the boundaries of the bubbles and would not cause an opaque appearance (col. 4 ln 40 – 46) as disclosed in Kolta. The size of the microbubbles for example compositions of the present invention were measured by a flow impedence device and could not be measured with a laser diffraction device (page 18 ln 1-6). The microbubbles of the present invention are described as being smaller than the bubbles released in a carbonated beverage, where a high proportion of the bubbles are not visible (page 6 ln 12-18). The bubbles formed upon the release of the pressure upon exposure to air in Kolta are necessarily large and are not microbubbles. As stated by the Examiner, Kolta teaches that the gelatin and the oxygen have a synergistic effect. As stated in Kolta, "**Oxygen transport** to deeper levels **is facilitated if the gelling agent**, from which the gel has been made, has components that can be absorbed by living tissues, and metabolism is further facilitated if the gelling agent can be utilized by eucariotic cells". Furthermore, Kolta teaches away from oxygen alone being able to heal tissue, stating, "We have supposed that during the absorption of proloxin the oxygen supply alone does not support the process of crating new tissues to a sufficient extent" (col. 14 ln 1-3). This synergistic effect can not be present in the superoxygenated composition of the present invention because it lacks the gelatin. Therefore, the composition of Kolta that teaches a synergistic effect without microbubbles can not obviate or motivate a superoxygenated composition which lacks the important synergistic component when Kolta teaches that oxygen alone is insufficient to promote heeling.

With respect to treatment of anaerobe bacteria, Kolta states that "The intensive presence of oxygen will prevent proliferation of anaerobe bacteria which otherwise would rapidly multiply in the gelatin" (col. 2 ln 12+) as pointed out by the examiner. Kolta begins the disclosure (col. 1 ln 10-24) by describing how gelatin normally promotes the proliferation of anerobe bacteria, stating, "It has been known for a long time that ossein-products like gelatin alba are excellent base materials for different kinds of pharmaceuticals. In room temperature the water based solution of such materials forms a gel if the concentration exceeds about 1-1.5%. It is also known that gels, especially gelatin can be used for treating different kinds of skin wounds, e.g.

burns or frost wounds. The gel is applied under a cover primarily for treating *combustio erythematosa*. It is also well-known in the art that gels, particularly gelatin are ideal media for bacterial cultures, and in the treatment of burn or frost wounds there is a dilemma whether gelatin can be used at all and whether such use should take place under a cover or not. The primary problem connected with a covered treatment lies in the potential danger of the proliferation of anaerobe bacteria." The storage of the gel in an oxygen rich form would keep anaerobe bacteria from getting into the gel prior to its introduction to the wound. Kolta does not disclose that the oxygen in the gel attacks anaerobe bacteria infections present in the wound, only that it will prevent their proliferation in the gel.

Therefore, one can not combine Kolta, which requires synergistic components not present in the present invention and does not teach that the treatment with the gel will kill anaerobe bacteria infections, with Ladin and White, which does not teach microbubbles or a superoxygenated composition, to render obvious the present invention which claims a method using a superoxygenated composition of oxygen microbubbles. Applicants respectfully request that claims 1, 2, 4-7, 10, 11, and 13-21 be allowed.

Applicants have made every effort to present claims that distinguish over the cited art, and it is believed that all claims are in condition for allowance. However, Applicants invite the Examiner to call the undersigned if it is believed that a telephonic interview (direct line (561) 671-3656) would expedite the prosecution of the application to an allowance. Although no fee is believed to be due, the Commissioner for Patents is hereby authorized to charge any deficiency in fees due or credit an excess in fees with the filing of the papers submitted herein during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,
AKERMAN SENTERFITT

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